This Page Is Inserted by IFW Operations and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.

CLAIMS

What is claimed is:

1. A pyrimidine derivative of the formula (I)

$$\begin{array}{c|c}
Q_1 \\
N \\
N \\
Q_2
\end{array}$$

$$\begin{array}{c|c}
Q_2 \\
R^1 \\
R^1
\end{array}$$
(I)

wherein

5

R¹ is selected from hydrogen, (1-6C)alkyl [optionally substituted by one or two substituents independently selected from halo, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, hydroxy, cyano, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl, -NHCO(1-4C)alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], N-phthalimido-(1-4C)alkyl, (3-5C)alkynyl [optionally substituted by one phenyl substituent] and (3-6C)cycloalkyl-(1-6C)alkyl;

wherein any phenyl or benzyl group in R¹ is optionally substituted by up to three substituents independently selected from halogeno, hydroxy, nitro, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, cyano, trifluoromethyl, (1-3C)alkyl [optionally substituted by 1 or 2 substituents independently selected from halogeno, cyano, amino, (1-3C)alkylamino, di-[(1-3C)alkyl]amino, hydroxy and trifluoromethyl], (3-5C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (3-5C)alkynyl, (1-3C)alkoxy, -SH, -S-(1-3C)alkyl, carboxy, (1-3C)alkoxycarbonyl; Q₁ and Q₂ are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-tetrahydronaphthyl;

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula (Ia) and Q_2 may optionally bear on any available carbon atom further substituents of the formula (Ia)

$$(CH_2)n \longrightarrow (CH_2)m \longrightarrow Z$$

[provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the -NH-link];

wherein

5

X is CH₂, O, S, NH or NRx [wherein Rx is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4Calkoxy or hydroxy];

Y is H or as defined for Z:

Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino;

15 n is 1, 2 or 3; m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],

- 20 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,
- 25 N.N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H2N-CO-NH-),

- (1-4C)alkylNH-CO-NH-. di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;
- and also independently, or in addition to, the above substituents, Q₁ may optionally bear on any available carbon atom up to two further substituents independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;
- and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl, di-[(
- 20 4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkyl, alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl,
- 25 morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino,
 - (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy,
 - \underline{N} -(1-4C)alkylcarbamoyl-(1-4C)alkoxy, $\underline{N},\underline{N}$ -di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy,
 - 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy, 2-di-[(1-4C)alkyl]aminoethoxy,
- 30 (1-4C)alkoxycarbonyl-(1-4C)alkoxy, halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy, 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy,

tetrahydronaphthyl;

- (3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H-N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-, di-[(1-4C)alkyl]N-CO-5 N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q2 may optionally bear on any available carbon atom up to two further substituents independently selected from (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, 10 benzoyl, phenoxy, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio, phenoxy and phenyl-(1-4C)alkoxy substituents may optionally bear up to five 15 substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.
- A pyrimidine derivative of the formula (I) as claimed in claim 1, wherein
 R¹ is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally
 substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
 Q₁ and Q₂ are independently selected from phenyl, naphthyl, indanyl and 1,2,3,4-
- 25 and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link];
- X is CH₂, O, S, NH or NRx [wherein Rx is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4Calkoxy or hydroxy];

 Y is H or as defined for Z;

Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino; n is 1, 2 or 3; m is 1, 2 or 3;

5

and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,

fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,

N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-

15 (1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-

(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkylthio,

(1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-

(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H2N-CO-NH-),

(1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-,

di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino,
(2-4C)alkanoylamino;

and also independently, or in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from

25 (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl, phenylthio and

30 phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy;

)

and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,

- fluoro-(1-4C)alkyl, amino-(1-3C)alkyl, (1-4C)alkylamino-(1-3C)alkyl, di-[(1-4C)alkyl]amino-(1-3C)alkyl, cyano-(1-4C)alkyl, (2-4C)alkanoyloxy-(1-4C)-alkyl, (1-4C)alkoxy-(1-3C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl,
- N,N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkyl, pyrrolidin-1-yl-(1-3C)alkyl, piperidin-1-yl-(1-3C)alkyl, piperazin-1-yl-(1-3C)alkyl, morpholino-(1-3C)alkyl, thiomorpholino-(1-3C)alkyl, piperazin-1-yl, morpholino, thiomorpholino, (1-4C)alkoxy, cyano-(1-4C)alkoxy, carbamoyl-(1-4C)alkoxy, N-(1-4C)alkylcarbamoyl-(1-4C)alkoxy, N-di-[(1-4C)alkyl]-carbamoyl-(1-4C)alkoxy, 2-aminoethoxy, 2-(1-4C)alkylaminoethoxy,
- halogeno-(1-4C)alkoxy, 2-hydroxyethoxy, (2-4C)alkanoyloxy-(2-4C)alkoxy, 2-(1-4C)alkoxyethoxy, carboxy-(1-4C)alkoxy, (3-5C)alkenyloxy, (3-5C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphinyl, (1-4C)alkylsulphonyl, hydroxy-(2-4C)alkylthio, hydroxy-(2-4C)alkylsulphinyl, hydroxy-(2-4C)alkylsulphonyl, ureido (H₂N-CO-NH-), (1-4C)alkylNH-CO-NH-, di-[(1-4C)alkyl]N-CO-NH-, (1-4C)alkylNH-CO-N[(1-4C)alkyl]-,

2-di-[(1-4C)alkyl]aminoethoxy, (1-4C)alkoxycarbonyl-(1-4C)alkoxy,

- di-[(1-4C)alkyl]N-CO-N[(1-4C)alkyl]-, carbamoyl, N-[(1-4C)alkyl]carbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino,
 - and also independently, or in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from
- 25 (3-8C)cycloalkyl, phenyl-(1-4C)alkyl, phenyl-(1-4C)alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-(1-4C)alkyl,
- 30 phenylthio, phenoxy and phenyl-(1-4C)alkoxy substituents may optionally bear up to five substituents independently selected from halogeno, (1-4C)alkyl and (1-4C)alkoxy; or a

pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

- 3. A pyrimidine derivative of the formula (I) as claimed in claim 1 or 2, wherein R¹ is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
 - Q_1 and Q_2 are independently selected from phenyl or indanyl; and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the
- 10 formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link];
 - X is CH₂, O, S, NH or NRx [wherein Rx is (1-4C)alkyl, optionally substituted by one substituent selected from halo, amino, cyano, (1-4Calkoxy or hydroxy];
- Y is H or as defined for Z;
 Z is OH, SH, NH₂, (1-4C)alkoxy, (1-4C)alkylthio, -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂,
 -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl], morpholino or thiomorpholino;
 n is 1, 2 or 3; m is 1, 2 or 3;
- and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino;
- and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino,
- 30 and also independently, or in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from

phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

- 4. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 3, wherein 5 R¹ is hydrogen, benzyl, (3-5C)alkynyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-4C)alkyl [optionally substituted by one or two substituents independently selected from hydroxy, amino, halo, trifluoromethyl and cyano] or (3-5C)alkenyl substituted by one to three halo groups or one phenyl substituent;
 - Q₁ and Q₂ are independently selected from phenyl or indan-5-yl;
- and one or both of Q₁ and Q₂ bears on any available carbon atom one substituent of the formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link];
- X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2;
 - and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
- 20 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino; and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent],
- 25 (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or
- 30 in-vivo-hydrolysable ester thereof.

- 5. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 4, wherein R¹ is -CH₂CH=CHBr, -CH₂CH₂CH₂CF₃ or -CH₂CH=CH-phenyl;
- Q_1 and Q_2 are independently selected from phenyl or indan-5-yl;

and one or both of Q, and Q2 bears on any available carbon atom one substituent of the

- 5 formula (Ia) and Q₂ may optionally bear on any available carbon atom further substituents of the formula (Ia) [provided that when present in Q₁ the substituent of formula (Ia) is not adjacent to the -NH- link];
 - X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or
- 10 (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2; and Q₁ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,
- fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino; and Q₂ may optionally bear on any available carbon atom up to four substituents independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl,
- 20 fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.

25

- 6. A pyrimidine derivative of the formula (I) as claimed in any of claims 1 to 5, wherein R¹ is -CH₂CH=CHBr, -CH₂CH₂CF₃ or -CH₂CH=CH-phenyl;
- Q_1 and Q_2 are both phenyl;
- Q₁ bears on any available carbon atom one substituent of the formula (Ia) [provided that the 30 substituent of formula (Ia) is not adjacent to the -NH- link];

X is O; Y is H or OH and Z is -NH(1-4C)alkyl, -N[(1-4C)alkyl]₂, -NH-(3-8C)cycloalkyl, pyrrolidin-1-yl or piperazin-1-yl [optionally substituted in the 4-position by (1-4C)alkyl or (1-4C)alkanoyl]; n is 1 or 2 and m is 1 or 2;

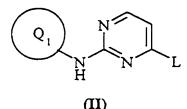
and Q_1 may optionally bear on any available carbon atom up to four substituents

- independently selected from halogeno, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino; and Q₂ may optionally bear on any available carbon atom up to four substituents
- 10 independently selected from halogeno, hydroxy, thio, nitro, carboxy, cyano, (2-4C)alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], (2-4C)alkynyl, (1-5C)alkanoyl, (1-4C)alkoxycarbonyl, (1-6C)alkyl, hydroxy-(1-6C)alkyl, fluoro-(1-4C)alkyl, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoylamino, and also independently, or in addition to, the above optional substituents, Q₂ may optionally bear on any available carbon atom up to two further substituents independently selected from phenylthio, phenyl, phenoxy and benzimidazol-2-yl; or a pharmaceutically-acceptable salt or
- 7. A pyrimidine derivative of the formula (I) as described in claim 5 or 6, other than that 20 R¹ is H; or a pharmaceutically-acceptable salt or in-vivo-hydrolysable ester thereof.
 - 8. A pyrimidine derivative of the formula (I) as claimed in claim 1, being: 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-bromo-4-methylanilino)pyrimidine;
- 25 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-
 - (2,5-dichloroanilino)pyrimidine;

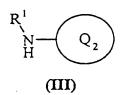
in-vivo-hydrolysable ester thereof.

- 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-
- (3,4-dichloroanilino)pyrimidine;
- 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,4-difluoro-
- 30 (N-cyanomethyl)anilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-

- 2-fluoroethyl)anilino)pyrimidine;
- 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-propyn-2-yl)anilino)pyrimidine;
- 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-
- 5 (N-cyanomethyl)anilino)pyrimidine;
 - 2-{4-[3-(*N*,*N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methylanilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-cyanoanilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-
- 10 (N-2,2-difluoroethyl)anilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-4,4,4-trifluorobutyl)anilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2,5-dichloro-(N-3-phenylprop-2-enyl)anilino)pyrimidine;
- 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methyl-(N-4,4,4-trifluorobutyl)anilino)pyrimidine;
 - 2-{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methyl-(N-3-bromoprop-2-enyl)anilino)pyrimidine;
 - $2-\{4-[3-(N,N-Dimethyl)amino-2-hydroxy-propoxy] anilino\}-4-(2-fluoro-5-methyl-(N-3-nethyl-N-3-neth$
- 20 phenylprop-2-enyl)anilino)pyrimidine;
 or pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof.
 - 9. A process for the preparation of a compound of the formula (I) as claimed in claim 1, which comprises of a) to h):-
- 25 a) reacting a pyrimidine of formula (II):



wherein L is a displaceable group as defined below, with a compound of formula (III):



b) reaction of a pyrimidine of formula (IV):

$$\begin{array}{c|c}
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\
 & & \\$$

wherein L is a displaceable group as defined below, with a compound of formula (V):

10

5

c) for compounds of formula (I) wherein n is 1, 2 or 3; m = 1 and Y is OH, NH_2 or SH: reaction of a 3-membered heteroalkyl ring of formula (VI):

$$(CH_2)_n$$

$$X$$

$$Q_1$$

$$M$$

$$N$$

$$Q_2$$

$$Q_1$$

$$M$$

$$R^1$$

$$(VI)$$

15 wherein A is O, S or NH;

with a nucleophile of formula (VII):

Z-D

(VII)

wherein D is H or a suitable counter-ion;

d) for compounds of formula (I) where X is oxygen: reaction of an alcohol of formula (VIII):

HO
$$Q_1$$
 N Q_2 Q_2 Q_3 Q_4 Q_2 Q_3 Q_4 Q_5 Q_5 Q_7 Q_8 Q_8

5 with an alcohol of formula (IX):

$$Z$$
 $(CH_2)_m$
 $(CH_2)_n$
 OH
 (IX)

e) for compounds of formula (I) wherein X is CH₂, O, NH or S; Y is OH and m is 2 or 3:

10 reaction of a compound of formula (X):

$$LgO \longrightarrow (CH_2)m$$

$$(CH_2)_n$$

$$X$$

$$Q_1$$

$$M$$

$$N$$

$$R^1$$

$$(X)$$

- wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula Z-D (VII) wherein D is H or a suitable counter-ion;
 - f) for compounds of formula (I) wherein X is CH_2 , O, NH or S; Y is H; n is 1, 2 or 3 and m is 1, 2 or 3: reaction of a compound of formula (XI):

$$\begin{array}{c|c} LgO \longrightarrow (CH_2)m & (CH_2)_n \\ X & Q_1 & N & Q_2 \\ & & & & & \\ & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\$$

wherein -OLg is a leaving group such as mesylate or tosylate; with a nucleophile of formula 5 Z-D (VII) wherein D is H or a suitable counter-ion;

g) for compounds of formula (I) wherein X is O, NH or S; Y is H; n is 1, 2 or 3 and m is 1, 2 or 3: reaction of a compound of formula (XII) with a compound of formula (XIII):

or

10

- 15 h) for compounds of formula (I) in which Z is SH, by conversion of a thioacetate group in a corresponding compound; and thereafter if necessary:
 - i) converting a compound of the formula (I) into another compound of the formula (I);
 - ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester; wherein L is a 20 displaceable group and D is hydrogen or a counter-ion.
 - 10. A method for producing an anti-cancer effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the formula (I)

PCT/GB99/02790

10

as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

- 11. A compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically5 acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.
 - 12. The use of a compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm blooded animal.
 - 13. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claims 1 to 8, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.